32

Claims

5

10

15

1. A polymer comprising a polymeric backbone comprising at least one unit having the structure (I),

wherein R-R⁴ comprise groups selected from the group consisting of H, C₁-C₁₂ alkyl, C₆-C₁₈ aryl, C₇-C₁₈ aralkyl, C₆-C₁₈ cycloalkyl or any of the group consisting of C₁-C₁₂ alkyl, C₆-C₁₈ aryl, C₇-C₁₈ aralkyl, C₆-C₁₈ cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms; R and R² or R and R⁴ or R and R¹ or R² and R³ may be joined so that with the carbon atom(s) to which they are attached they together form a saturated, partially unsaturated or unsaturated ring system respectively, may have a pendent group which may incorporate a linker unit, (for example a peptide linkage or a unit having the structure (I); A comprises a proton donating moiety selected from the group consisting of

B comprises a hydrolytically labile group and is selected from the group consisting of

$$\begin{bmatrix}
0 \\
0
\end{bmatrix}, \begin{bmatrix}
0 \\
0
\end{bmatrix}, \begin{bmatrix}
NH \\
N \\
N \\
R^5
\end{bmatrix}$$
30
$$\begin{bmatrix}
0 \\
N \\
N \\
R^5
\end{bmatrix}, \begin{bmatrix}
0 \\
N \\
N \\
N \\
R^5
\end{bmatrix}$$

33

wherein each R^5 is individually selected from the group consisting of H, C_1 - C_{12} alkyl, C_6 - C_{18} aryl, C_7 - C_{18} aralkyl, C_6 - C_{18} cycloalkyl; wherein groups A and B are in a cis-configuration about bond C_a - C_b ; m is an integer of 0 to 100, n, p and q are each an integer of 0 or 1; Q comprises 1 or more structures selected from the group consisting of

$$\begin{bmatrix}
0 \\
R^{8}
\end{bmatrix}, \begin{bmatrix}
1 \\
N
\end{bmatrix}, \begin{bmatrix}
0 \\
0
\end{bmatrix}, \begin{bmatrix}
0 \\
0
\end{bmatrix}, \begin{bmatrix}
N \\
N
\end{bmatrix}, \begin{bmatrix}
N \\
R^{7}
\end{bmatrix}$$

$$\begin{bmatrix}
0 \\
R^{7}
\end{bmatrix}, \begin{bmatrix}
S \\
R^{11}
\end{bmatrix},$$

10

5

wherein R⁶-R¹¹ are individually selected from the same group as defined for group R above and r is an integer between 1 and 5000, and wherein the other components of the polymeric backbone may be other groups having the structure (I), peptide units or degradable polymeric, oligomeric or monomeric units.

2. A polymer according to claim 1, wherein C_a - C_b is a double bond and p and q are each 0.

541 640

30

15

- 3. A polymer according to claim 1 or 2, wherein R, R² and R³ are selected from the group consisting of hydrogen, methyl, ethyl or propyl, preferably hydrogen.
- 4. A polymer according to any preceding claim, wherein A is a carboxylic acid group.
- 5. A polymer according to any preceding claim, wherein B comprises an amide bond
- 6. A polymer according to any preceding claim, wherein Q comprises a carbonyl funtionality.
 - 7. A polymer according to any preceding claim, wherein the polymeric backbone additionally comprises polymers selected from the group consisting of acrylic polymers, alkylene polymers, urethane polymers, amide polymers (including polypeptides), polysaccharides and ester polymers.
 - 8. A polymer according to any preceding claim, wherein the polymeric backbone comprises polymers selected from the group consisting of derivatised polyethyleneglycol and copolymers of

hydroxyalkyl(meth)acrylamide, most preferably amine derivatised polyethyleneglycol or hydroxypropylmethacrylamide-methacrylic acid copolymers or amide or ester derivatives thereof.

9. A polymer according to any preceding claim, wherein the polymeric backbone comprises the structure (II)

10

5

wherein A, B, Q, R-R⁴, m, n, p and q are as defined in any preceding claim; L is a polymeric, oligomeric or copolymeric bridging group which comprises polymer selected from the group consisting of acrylic polymers, alkylene polymers, urethane polymers, polyethylene glycols, polyamides,

polysaccharides and polyesters; a is an integer of 1 to 100000, b and c are integers of 0 to 100000 and s is an integer of 0 to 100; D comprises one or more structures individually selected from the group consisting of,

$$\begin{bmatrix}
R^{14} \\
R^{14}
\end{bmatrix}$$

$$\begin{bmatrix}
R^{14} \\
R^{15}
\end{bmatrix}$$

$$\begin{bmatrix}
R^{14} \\
R^{14}
\end{bmatrix}$$

$$\begin{bmatrix}
R^{14} \\
R^{15}
\end{bmatrix}$$

20

15

wherein R¹⁴ and R¹⁴ comprise groups individually selected from the same groups as defined for R or may comprise a structure selected from the group consisting of

30

25

wherein n is an integer of 0-100, R^{15} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl, R^{16} to R^{18} are individually selected from the group

5

10

consisting of H, C_1 - C_{12} alkyl, C_1 - C_{12} alkenyl, C_6 - C_{18} aryl, C_7 - C_{18} aralkyl, C_5 - C_{18} cycloalkyl or is selected from the group consisting of C_1 - C_{12} alkyl, C_1 - C_{12} alkenyl, C_6 - C_{18} aryl, C_7 - C_{18} aralkyl, C_6 - C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms, a pendent group comprising a linker unit, for example a peptide linkage or a unit having the structure (I) or a leaving group; R^{13} is selected from the group consisting of H, C_1 - C_{12} alkyl, C_1 - C_{12} alkenyl, C_6 - C_{18} aryl, C_7 - C_{18} aralkyl, C_5 - C_{18} cycloalkyl or is selected from the group consisting of C_1 - C_{12} alkyl, C_1 - C_{12} alkenyl, C_6 - C_{18} aryl, C_7 - C_{18} aralkyl, C_6 - C_{18} cycloalkyl substituted, within the carbon chain or appended thereto, with one or more heteroatoms, R^{13} optionally incorporating a linker unit, for example a peptide linkage or a unit having the structure (I).

10. A polymer according to claim 9, wherein L comprises amine derivatised polyethyleneglycol, most preferably a structure selected from the group consisting of

$$\begin{bmatrix}
H & O & H & PEG & H & O & H \\
R^{19} & R^{20}
\end{bmatrix}$$

$$\begin{bmatrix}
H & O & H & O & H & O \\
R^{21} & O & PEG & O & H \\
R^{21} & R^{22}
\end{bmatrix}$$

$$\begin{bmatrix}
H & O & H & O & H & O & H \\
R^{21} & PEG & H & O & NH & O & H \\
R^{23} & O & O & R^{24}
\end{bmatrix}$$

wherein PEG is polyethyleneglycol, R¹⁹-R²⁴ optionally incorporates a pendent group comprising a cleavable linker unit, and may additionally comprise groups individually selected from the same groups as defined for R or may comprise a structure selected from the group consisting of

25
$$N_2$$
 N_1
 N_2
 N_1
 N_1
 N_1
 N_2
 N_1
 N_1
 N_1
 N_1
 N_2
 N_1
 N_1
 N_1
 N_1
 N_2
 N_1
 N_1
 N_1
 N_1
 N_1
 N_1
 N_1
 N_2
 N_1
 N_2
 N_1
 N

wherein n and R¹⁶ to R¹⁸ and R¹⁶ to R¹⁸ are as defined in claim 9.

10. A polymer according to claim 9 or 10, wherein s is an integer of 1 to 10, preferably 1.

12. A polymer according to claim 9, 10 or 11, wherein at least one of R¹⁴

WO 01/17515

5

10

15

20

to R²⁴ incorporates a cleavable bond, preferably a group (I) or one or more peptide bonds.

- 13. A polymer according to any preceding claim, wherein the polymer is conjugated to a bioactive agent, preferably an anti cancer agent, most preferably, doxorubicin, daunomycin or taxol.
- 14. A polymer according to any preceding claim, wherein the molecular weight is in the range 0.5kDa-400kDa.
- 15. A polymer according to any preceding claim, having the structure

wherein PEG is a polyethylene glycol group, or derivative thereof, having a molecular weight in the range 500 Da-100kDa and u is an integer in the range of 1-10000.

16. A polymer according to any of claims 1 to 14, having the structure

wherein PEG is a polyethylene glycol group having a molecular weight in the range 500 Da-100kDa or derivative thereof, and u is an integer in the range of 1-10000.

A prepolymer comprising the structure

wherein A, B, Q, R-R³, m, n, p and q are as defined in any preceding claim;
R¹³ and L are as defined in any of claims 9 to 16; A', B', Q' R¹-R⁴', m', n', p',
and q' are selected from the groups as defined for A, B, Q, R R⁴ m, n, p and
q respectively; E and K are selected from the group consisting of hydrogen,

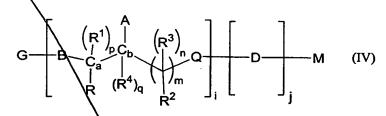
an\activating group or a protecting group and may be the same or different: z is an integer of 1 to 100, y is an integer of 0 to 10 and x is an integer of 0 to 100.

18. A prepolymer according to claim 17, wherein z is 1, y is 1 and x is 1. A prepolymer according to claim 17 or 18, wherein B and B' comprise a carboxyl group and E and K are selected from the group consisting of hydrogen, N-succinimidyl pentachlorophenyl, pentaflourophenyl, paranitrophenyl, dinitrophenyl, N-phthalimido, N-norbornyl, cyanomethyl,

pylidyl, trichlorotriazine, 5-chloroquinoline, preferably hydrogen or N-

succinimidyl.

20. A prepalymer comprising the structure (IV)



15

20

10

wherein A, B, Q, R-R⁴, m,\n, p and q are as defined in any preceding claim; D si as defined in any of claims 9 to 16; G and M are selected from the group consisting of hydrogen, an activating group or a protecting group, i and j are integers of 1 to 10.

21. A prepolymer according to claim 20, wherein i is 1 and j is 1.

A prepolymer according to claim 20 or 21, wherein B and D comprise carboxylic acid groups and G and M are selected from the group consisting of hydrogen, N-succinimidyl pentachlorophenyl. 25 pentaflourophenyl, para-nitrophenyl, dinitrophenyl, N-phthalimido, Nnorbornyl, cyanomethyl, pyridyl, trichlorotriazine, 5-chloroquinoline,

23. A process for preparing a polymer, copolymer or prepolymer comprising reacting at least one compound having the structure (V)

preferably hydrogen or N-succinimidyl.

WO 01/17515 PCT/US00/24232

38

5

10

wherein R²⁵, R²⁶ and R²⁷ are selected from the group as defined for R; Q" is selected from the group consisting of carboxylic acid, primary or secondary amine carbonyl; u is an integer of 0 or 1, v is an integer of 1 to 100, R²⁷ and R²⁵ may be attached to form part of a C₃ - C₁₂ ring system which may have more than one unsaturated bond and may be aromatic; with at least one compound selected from the group consisting of J and R¹³LNHR²⁸, wherein L and R¹³ groups are as defined above and R²⁸ is selected from the same group as defined for R and may be the same or different, J is a compound having at least one primary or secondary amine and a carboxylic acid group and a pendent group incorporating a cleavable bond.

SAS 3

15

- A method of selectively degrading a polymer comprising the steps of:
 - introducing a polymer as comprising a structure (I) or (II) as defined in any preceding claim, to an environment having a pH of less than 6.5,

20

- b) \ cleaving said polymer.
- 25. A method for releasing a bioactive agent comprising the steps of
 - a) introducing a conjugate comprising a structure (I) or (II) as defined in any preceding claim, and a bioactive agent to an environment having a pH of less than 6.5,

25

30

- c) cleaving the bioactive agent from the linker group by acid or enzymic hydrolysis,
- d) optionally additionally cleaving the polymer by acid or enzymic hydrolysis.
- 26. A composition comprising at least one polymer as defined in any of claims 1 to 16 and a carrier.
- 27. A composition comprising at least one polymer as defined in any of claims 1 to 16 and a pharmaceutically acceptable excipient.
- 28. Use of a polymer as defined in any of claims 1 to 16 as a

WO 01/17515

PCT/US00/24232

39

pharmaceutical excipient.